2026 Clinical Practice Guideline Update by the Infectious Diseases Society of America on the Treatment and Management of COVID-19: Antiviral Treatment for Mild to Moderate COVID-19 in Infants, Children, and Adolescents

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ABSTRACT. This article provides a focused update to the clinical practice guideline on the treatment and management of patients with COVID-19, developed by the Infectious Diseases Society of America. The guideline panel presents eight new recommendations on the use of nirmatrelvir/ritonavir and remdesivir in pediatric patients with mild to moderate COVID-19. The recommendations are based on evidence derived from a systematic literature review and adhere to a standardized methodology for rating the certainty of evidence and strength of recommendation according to the GRADE (Grading of Recommendations, Assessment, Development, and Evaluation) approach.

Keywords. COVID-19; SARS-CoV-2; antivirals; guideline; pediatric

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In adolescents (age 12 to <18 years) with mild to moderate COVID-19, does treatment with nirmatrelvir/ritonavir vs. no treatment result in better outcomes (e.g., time to symptom resolution, hospitalization, progression to severe or critical illness)?

Recommendation: In adolescents with mild to moderate COVID-19 at high risk for progression to severe disease (Table 1), the IDSA guideline panel recommends nirmatrelvir/ritonavir over no antiviral treatment (*strong recommendation, moderate certainty of evidence*).

Remarks:

- Although the U.S. Food and Drug Administration (FDA) has approved nirmatrelvir/ritonavir for mild to moderate COVID-19 in adults, it is not approved for pediatric use. The FDA has issued an Emergency Use Authorization (EUA) for nirmatrelvir/ritonavir for treatment of mild to moderate COVID-19 within 5 days of symptom onset in adolescents (age 12 to <18 years) who weigh ≥40 kg and are at high risk for progression to severe disease.

- Patients' medications should be screened for serious drug interactions.
- Dosing based on renal function:
    - Estimated glomerular filtration rate (eGFR) >60 ml/min: 300 mg nirmatrelvir/100 mg ritonavir every 12 hours for 5 days.
    - eGFR <60 mL/min and ≥30 mL/min: 150 mg nirmatrelvir/100 mg ritonavir every 12 hours for 5 days.
    - eGFR <30 mL/min including hemodialysis: 300 mg nirmatrelvir/100 mg ritonavir once on day 1, followed by 150 mg nirmatrelvir/100 mg ritonavir once daily on days 2-5.

Recommendation: In adolescents with mild to moderate COVID-19 who have several factors associated with increased but not high risk for progression to severe disease (Table 2), the IDSA guideline panel suggests nirmatrelvir/ritonavir over no antiviral treatment (*conditional recommendation, low certainty of evidence*).

Remarks:

- Patients and families who place a higher value on avoiding adverse events and/or drug-drug interactions and a lower value on the small reduction in hospitalization risk or faster symptom resolution observed in adult studies may reasonably decline nirmatrelvir/ritonavir.

Recommendation: In adolescents with mild to moderate COVID-19 who have no risk factors or only 1 factor associated with increased but not high risk for progression to severe disease (Table 2), the IDSA guideline panel suggests against use of nirmatrelvir/ritonavir (*conditional recommendation, low certainty of evidence*).

In infants (age <12 months), children (age 12 months to <12 years), or adolescents (age 12 to <18 years) with mild to moderate COVID-19, does treatment with remdesivir vs. no treatment result in

better outcomes (e.g., time to symptom resolution, hospitalization, progression to severe or critical illness)?

Recommendation: In infants, children, or adolescents with mild to moderate COVID-19 at high risk for progression to severe disease (Table 1), the IDSA guideline panel recommends remdesivir over no antiviral treatment (*strong recommendation, moderate certainty of evidence*).

Remarks

- Remdesivir has demonstrated benefit in outpatient adults with COVID-19, so it is reasonable to extrapolate a potential benefit to pediatric patients at highest risk of disease progression despite limited studies in this population.
- Dosing:
    - Neonates weighing ≥1.5 kg (very limited data available for preterm neonates): Use lyophilized powder only. Loading dose 2.5 mg/kg on day 1, followed by 1.25 mg/kg dose once daily on days 2 and 3.
    - Infants, children, and adolescents:
        - 1.5 to <3 kg: Use lyophilized powder only. Loading dose 2.5 mg/kg on day 1, followed by 1.25 mg/kg/dose once daily on days 2 and 3.
        - 3 to <40 kg: Use lyophilized powder only. Loading dose 5 mg/kg on day 1, followed by 2.5 mg/kg/dose once daily on days 2 and 3.
        - ≥40 kg: Use injection solution or lyophilized powder. Loading dose 200 mg on day 1, followed by 100 mg once daily on days 2 and 3.

Recommendation: In infants with mild to moderate COVID-19 who have any factor(s) associated with increased but not high risk for progression to severe disease (Table 2), the IDSA guideline panel suggests remdesivir over no antiviral treatment (*conditional recommendation, low certainty of evidence*).

Remarks

- Compared with older children and adolescents, infants are at increased risk of progression to severe COVID-19.
- Patients and families who place a higher value on avoiding daily infusions for 3 days and a lower value on the small reduction in hospitalization risk or faster symptom resolution may reasonably decline remdesivir.

Recommendation: In children or adolescents with mild to moderate COVID-19 who have several factors associated with increased but not high risk for progression to severe disease (Table 2), the IDSA guideline panel suggests remdesivir over no antiviral treatment (*conditional recommendation, low certainty of evidence*).

Remarks:

- Patients and families who place a higher value on avoiding daily infusions for 3 days and a lower value on the small reduction in hospitalization risk or faster symptom resolution may reasonably decline remdesivir.

Recommendation: In children or adolescents with mild to moderate COVID-19 who have only 1 factor associated with increased but not high risk (Table 2), the IDSA guideline panel suggests against use of remdesivir (*conditional recommendation, low certainty of evidence*).

Recommendation: In infants, children, or adolescents with mild to moderate COVID-19 who have no risk factors for progression to severe disease (Tables 1 and 2), the IDSA guideline panel suggests against use of remdesivir (*conditional recommendation, low certainty of evidence*).

Tables 1 and 2 list examples of risk factors broadly categorized by medical condition or immunosuppressive treatment (adapted from Centers for Disease Control and Prevention [CDC] guidance "People with Certain Medical Conditions and COVID-19 Risk Factors" and pediatric meta-analyses and

systematic reviews) [Aparicio 2024, CDC Risk Factors, Harwood 2022]. Categorization is largely based on cohort data from the Omicron era and may not fully account for changes in population immunity or evolving variant characteristics.

The risk of progression to severe COVID-19 is a continuum influenced by various factors, including the severity of risk factors and/or immunosuppression. The categorization of risk and the examples provided in Tables 1 and 2 are illustrative and not exhaustive.

Table 1. Examples of factors associated with high risk of progression

Example health condition	Example therapeutics*
• Severe combined immunodeficiency syndrome • Congenital or acquired agammaglobulinemia (e.g., X-linked agammaglobulinemia) • Congenital or acquired profound lymphocyte dysfunction • Hematological malignancy on intensive therapy expected to cause prolonged, profound lymphopenia or antibody deficiency (e.g., acute leukemia during induction, treatment for relapsed/refractory disease, or recent immunotherapy) [Hashmi 2024] • HIV infection with CD4 <15% or <200 cells/mm^3 • Hematopoietic stem cell transplant (HSCT) <6 months or active graft versus host disease	• B-cell depleting agents in past 6 months (e.g., rituximab, blinatumomab) • T-cell depleting agents in past 12 months (e.g., alemtuzumab, high-dose cyclosporine, abatacept, anti-thymocyte globulin) • CAR-T therapy in past 12 months • Tyrosine kinase inhibitors (e.g., ibrutinib, acalabrutinib, others) • High-dose corticosteroids (≥20 mg [≥0.5 mg/kg] prednisone or equivalent for ≥4 weeks)
*Example therapeutics that predispose to substantial immunosuppression	

Table 2. Examples of factors associated with increased but not high risk of progression*

Example health condition	Example therapeutics+
• Chronic heart disease, cyanotic or otherwise hemodynamically significant • Chronic liver diseases • Chronic lung diseases other than asthma • Conditions associated with moderate immunocompromise (e.g., acute lymphoblastic leukemia in maintenance; solid tumors receiving conventional chemotherapy; HSCT >6 months prior; immunomodulatory therapy; solid organ transplantation) • Diabetes mellitus • End-stage renal disease • HIV with CD4 >200 cells/mm^3 • Neurodevelopmental conditions inclusive of Down syndrome • Obesity	• Anti-IL-6 • Anti-IL12 and 23 • Corticosteroids 10-20 mg (0.25-0.5 mg/kg) for ≥4 weeks

• Pregnancy (current or within 6 weeks of pregnancy) • Prematurity with ongoing sequelae affecting at least one organ system (e.g., chronic lung disease, neurodevelopmental sequelae) • Sickle cell disease	
*These factors vary in terms of the degree of risk they confer. For those that confer less risk, the benefit of antiviral therapy will likely be lower. +Example therapeutics that are less likely to predispose to substantial immunosuppression.	

166
167 ***BACKGROUND AND APPROACH TO RISK STRATIFICATION***
168
169 As in adults, classification of COVID-19 severity is helpful in targeting specific treatments to
170 disease stages for which benefit has been demonstrated in trials. Clinicians should determine severity of
171 illness according to the categories in Table 3. The scope of this guideline update is mild to moderate
172 COVID-19.
173
174 **Table 3.** Assessment of clinical severity of COVID-19 to target treatments

Severity of COVID-19
Mild-to-moderate COVID-19: SpO_2 >94% on room air and not needing supplemental oxygen*
Severe but not critical COVID-19: SpO_2 ≤94% on room air or needing low-flow supplemental oxygen
Critical COVID-19: Needing high-flow oxygen or non-invasive ventilation, mechanical ventilation, or ECMO
ECMO: Extracorporeal membrane oxygenation; **SpO_2**: Oxygen saturation *Treatment of mild-to-moderate COVID-19 is generally considered in people with risk factors for progression to severe disease, hospitalization, or death. Pediatric risk factors for severe COVID-19 are discussed above.

175
176 The clinical course of acute COVID-19 is typically less severe in children than in adults. Rates of
177 SARS-CoV-2 infection [CDC Demographic trends, Stokes 2020] and hospitalization [Kim 2020] are also
178 lower in children than in adults, and asymptomatic infection is more common [Han 2021, Chung 2021].
179 However, a subset of children with SARS-CoV-2 infection will progress to severe disease [Delahoy
180 2021, Siegel 2021, Wilde 2023, Williams 2021]. Among hospitalized pediatric patients, the percentage
181 requiring intensive care is comparable to that observed in hospitalized adults with COVID-19 [Aparicio
182 2024, Marks 2022, Swann 2020]. Therefore, careful risk stratification is essential to identify pediatric

patients at high risk of progression to severe disease who are most likely to benefit from antiviral therapy. Because mortality rates from COVID-19 are extremely low in children, mortality data were not considered. Hospitalization data were evaluated, and the panel's recommendations are primarily driven by the critical outcome of hospitalization. For hospitalization, risk categories were stratified into low risk, increased but not high risk, and high risk for progression to severe disease. Baseline risks for hospitalization in children were estimated as in adults for each category (0.5%, 3.0%, and 6.0%, respectively). The panel's rationale for deriving these estimations is described in a previous publication [Shumaker 2026]. Observational studies, summarized in meta-analyses and systematic reviews, have identified several key risk factors for severe COVID-19 in children [Aparicio 2024, Harwood 2022]. These can be broadly categorized as underlying health conditions, demographic factors, and prior immunological exposure.

Certain demographic factors correlate with disease severity [Antoon 2021, Holmes 2023, Saatci 2021, Swann 2020]. Several studies have shown age to be a key risk factor, with infants (<1 year) and adolescents (>12 years) at higher risk than young children [Aparicio 2024, CDC COVID-19 Response Team 2020, Dong 2020, Harwood 2022]. As a result, the panel's recommendations are stratified by age.

In addition to age, underlying medical conditions are the most significant predictors of severe disease and thus are a major factor for risk stratification in the panel's recommendations for antiviral treatment. These conditions include cardiac disease, neurologic disorders, prematurity (in young infants), diabetes, obesity (particularly if severe), chronic lung disease, and moderate or severe immunocompromise [Aparicio 2024, Harwood 2022]. Having multiple comorbidities is associated with higher risk than single conditions, and pediatric patients with multiple comorbidities are more likely to benefit from antiviral therapy.

It is important to consider, especially while implementing conditional recommendations, that the risk of disease progression comprises a continuum. The presence of various additional factors weighs toward higher risk and therefore likely greater benefit of antiviral treatment. Consistent with the finding that multiple comorbidities are associated with increased risk, markers of medical complexity, including

presence of a feeding tube, respiratory support, and other medical devices, are strongly associated with the risk of severe disease [Prodanuk 2025]. Although most pediatric studies have not evaluated the severity or degree of control of comorbidities, these are plausible contributors to risk. Additionally, lower socioeconomic status has been associated with increased disease severity, a pattern observed in many other infectious diseases [Bettenhausen 2017]. This disparity is likely driven by factors such as limited access to healthcare, crowded living conditions, and barriers to timely medical intervention [Beck 2015].

Finally, an important consideration in the overall risk of severe disease is the child's immunological status. Prior immunity, acquired through recent vaccination or SARS-CoV-2 infection, is associated with a reduced risk of severe disease, a protective effect that is also well-documented in adults. However, data are insufficient to precisely assess how risk changes based on factors such as number of vaccine doses, time since vaccination, time since infection, dominant SARS-CoV-2 variants, and ability to mount an immune response, particularly as these factors evolve over time at both individual and population levels.

Given the scarcity of clinical trial data on the treatment of COVID-19 in children, recommendations in these guidelines for management of non-hospitalized children are extrapolated largely from safety and efficacy data from clinical trial data in adults, as well as expert interpretation of other indirect evidence. Most children with mild or moderate COVID-19 without risk factors do not progress to more severe disease. As with adults, supportive care alone is recommended for these patients.

Treatment options for pediatric patients with mild to moderate COVID-19 who are deemed to be at high or increased risk for progression to severe disease are either nirmatrelvir/ritonavir within 5 days of symptom onset (for patients aged ≥12 years who weigh ≥40 kg) or remdesivir within 7 days of symptom onset (for patients of all ages).

Why is nirmatrelvir/ritonavir considered for treatment?

Nirmatrelvir/ritonavir combines nirmatrelvir, an inhibitor of SARS-CoV-2 main protease, with ritonavir, which increases levels of nirmatrelvir by inhibiting nirmatrelvir metabolism by cytochrome P450 3A4 (CYP3A4). Although the FDA has approved nirmatrelvir/ritonavir for adults age 18 and older

with mild-to-moderate COVID-19, the drug remains under EUA for high-risk adolescents aged 12 to <18 years and weighing ≥40 kg with mild-to-moderate COVID-19 [FDA EUA nirm/rit]. Under the EUA, nirmatrelvir/ritonavir must be initiated within 5 days of symptom onset. Nirmatrelvir/ritonavir is the only enteral antiviral available for COVID-19 treatment for adolescent patients. In the United States, molnupiravir is authorized under EUA only for patients ≥18 years of age due to animal studies that suggest harmful effects on bone and cartilage growth [FDA EUA Update August 9, 2024].

Why is remdesivir considered for treatment?

Remdesivir is a nucleoside analog prodrug, the active form of which is incorporated by viral RNA polymerase into nascent RNA chains, leading to premature RNA termination [Kokic 2021]. Remdesivir is the only antiviral available for COVID-19 treatment in infants and children <12 years of age or weighing <40 kg. The drug is approved by the FDA for patients of all ages, including term (estimated gestational age ≥37 weeks) neonates who weigh at least 1.5 kg.

METHODS

The panel's recommendations are based on evidence derived from systematic reviews and adhere to a standardized methodology for rating the certainty of evidence and strength of recommendation according to the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) approach (Supplementary Figure 1) [Guyatt 2008]. The recommendations have been endorsed by the Pediatric Infectious Diseases Society, Society for Healthcare Epidemiology, and the Society for Critical Care Medicine.

Strong recommendations ("the panel recommends") are made when the recommended course of action would apply to most people with few exceptions. Conditional recommendations ("the panel suggests") are made when the suggested course of action would apply to most people with many exceptions and shared decision making is important.

Literature reviews were conducted in September 2024 and June 2025. Key eligibility criteria at both the topic and clinical question levels guided the selection of studies for inclusion.

A critical appraisal of the evidence according to the GRADE (Grading of Recommendations Assessment, Development, and Evaluation) approach, along with an assessment of the benefits and harms of care options, informed the recommendation(s) [Guyatt 2008, IDSA Handbook]. Details of the systematic review and guideline development processes are available in the Supplementary Material.

NIRMATRELVIR/RITONAVIR

SUMMARY OF EVIDENCE FOR NIRMATRELVIR/RITONAVIR

The literature search identified three RCTs of nirmatrelvir/ritonavir for mild-to-moderate COVID-19 in adults that reported on the outcomes of hospitalization, serious adverse events, adverse events requiring discontinuation of treatment, and symptom resolution [Hammond 2022, Liu 2023, Hammond 2024, Hammond 2025] (Table 4, Supplementary Tables 1 and 2, Supplementary Figure 2). A phase 2/3 open-label, single-arm trial to assess the safety, pharmacokinetics, and efficacy of nirmatrelvir/ritonavir in patients aged <18 years with risk factors for severe COVID-19 is in progress [EPIC-Peds]. An investigation using electronic health record data from 8 health systems of nirmatrelvir/ritonavir prescribing between January 2022 and August 2023 showed that use was infrequent, with only 408 (2%) of 20,959 patients aged 12 to 17 years receiving a prescription within 4 days of their COVID-19 diagnosis [Bose-Brill 2024].

278 **Table 4.** GRADE Evidence Profile: In children with mild to moderate COVID-19, does treatment with nirmatrelvir/ritonavir vs. no treatment
279 result in better outcomes (e.g., time to symptom resolution, hospitalization, progression to severe or critical illness)?

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Nirmatrelvir / ritonavir	no nirmatrelvir / ritonavir*	Relative (95% CI)	Absolute (95% CI)		
Hospitalization (follow-up: 28 days)												
2[Hammond 2022, Hammond 2024]	randomized trials	not serious	not serious	serious[a]	serious[b]	none	13/1693 (0.8%)	0.5%	**RR 0.17** (0.10 to 0.31)	**4 fewer per 1,000** (from 5 fewer to 3 fewer)	⨁⨁◯◯ Low	CRITICAL
				serious[a]				3.0%		**25 fewer per 1,000** (from 27 fewer to 21 fewer)	⨁⨁◯◯ Low	
				not serious[a]				6.0%		**50 fewer per 1,000** (from 54 fewer to 41 fewer)	⨁⨁⨁◯ Moderate	
Serious adverse events												
3[Liu 2023, Hammond 2022, Hammond 2024]	randomized trials	not serious	not serious	not serious[a]	serious[b]	none	32/1895 (1.7%)	91/1881 (4.8%)	**RR 0.52** (0.20 to 1.35)	**23 fewer per 1,000** (from 39 fewer to 17 more)	⨁⨁⨁◯ Moderate	CRITICAL
Adverse events requiring discontinuation of treatment												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Nirmatrelvir / ritonavir	no nirmatrelvir / ritonavir*	Relative (95% CI)	Absolute (95% CI)		
3[Liu 2023, Hammond 2022, Hammond 2024]	randomized trials	not serious	not serious	not serious[a]	serious[b]	none	24/1895 (1.3%)	9/1881 (0.5%)	**RR 0.75** (0.5 to 1.13)	**26 fewer per 1,000** (from 53 fewer to 14 more)	⨁⨁⨁◯ Moderate	IMPORTANT
Symptom resolution for patients at high risk (follow-up: 28 days)[c]												
1[Hammond 2025]	randomized trials	not serious	not serious	not serious[a]	serious[d]	none	619/970 (63.8%)	566/986 (57.4%)	**HR 1.20** (1.07 to 1.35)	**67 more per 1,000** (from 25 more to 110 more)	⨁⨁⨁◯ Moderate	IMPORTANT
Symptom resolation for all patients (follow-up: 28 days)[e]												
1[Hammond 2025]	randomized trials	not serious	not serious	not serious[a]	serious[d]	none	619/970 (63.8%)	566/986 (57.4%)	**HR 1.20** (1.07 to 1.35)	**67 more per 1,000** (from 25 more to 110 more)	⨁⨁⨁◯ Moderate	IMPORTANT

CI: confidence interval; **HR:** hazard ratio; **RR:** risk ratio

*For hospitalization, percentages represent illustrative baseline risks for patients without risk factors for progression to severe disease, patients at increased but not high risk, and patients at high risk.

Explanations

a. Most trial participants were adults and evidence in pediatric patients is limited, reducing applicability to children. In addition, key trials were conducted in the pre-Omicron era and largely among unvaccinated, high-risk outpatients; current baseline risks and hospitalization patterns have changed substantially, which may affect applicability—particularly for lower-risk populations where hospitalizations are now rarer and less specific to COVID-19. Because the trial populations closely match those at highest risk today, the panel did not further downgrade for baseline-risk differences in the highest-risk stratum but did downgrade for indirectness in lower-risk strata.

b. Few events do not meet the optimal information size and suggest fragility in the estimate (Guyatt 2011).

c. Median time to resolution: NMV/r 16 days (95% CI: 15, 18) vs. placebo 19 days (95% CI: 18, 20).

d. 95% CI crossing threshold of meaningful difference; median time to resolution: 95% CI not completely separated.
e. Median time to resolution: NMV/r 16 days (95% CI: 15, 18) vs. placebo 19 days (95% CI: 18, 20) for EPIC-HR; 12 days (95% CI: 11, 13) vs. 13 (95% CI: 12, 14) in EPIC-SR

BENEFITS OF NIRMATRELVIR/RITONAVIR

In the EPIC-HR clinical trial that enrolled high-risk, unvaccinated adults, nirmatrelvir/ritonavir was associated with a relative risk reduction for hospitalization or death of 89% [Hammond 2022]. One large retrospective study of children aged 12-17 years found that use of nirmatrelvir/ritonavir was associated with a relative risk of hospitalization of 0.66 (95% CI: 0.56-0.71) [Wong 2024].

HARMS OF NIRMATRELVIR/RITONAVIR

Drug-drug interactions represent the most significant safety concern associated with nirmatrelvir/ritonavir. Ritonavir acts as a pharmacokinetic enhancer by inhibiting CYP3A4, thereby increasing plasma concentrations of nirmatrelvir. However, this same mechanism can lead to elevated levels of co-administered medications that are substrates of CYP3A4, potentially resulting in toxicity or adverse effects. Given the extensive list of medications affected, clinicians should carefully assess for interacting medications before prescribing [Paxlovid label]. Many drug-drug interactions can be mitigated by reducing the dose of or holding the interacting medication [Liverpool website].

Clinically significant adverse drug reactions were uncommon in controlled studies of nirmatrelvir/ritonavir in adults (Supplementary Figures 3 and 4). Dysgeusia (5%) and diarrhea (3%) are the most reported adverse reactions. Severe dermatological reactions such as Stevens-Johnson syndrome have also been reported [Paxlovid label]. A retrospective single-center chart review study identified presumed treatment-related adverse events in 2 of 92 adolescents who received nirmatrelvir/ritonavir [Lee 2025]. However, there are no controlled prospective studies of pediatric patients.

OTHER CONSIDERATIONS FOR NIRMATRELVIR/RITONAVIR

Other considerations for nirmatrelvir/ritonavir for children include renal function and available dosage forms for administration. Renal dosing for pediatric patients ≥12 years of age and ≥40 kg is based on estimated glomerular filtration rate (eGFR): no adjustment is needed for mild impairment (eGFR ≥60 mL/min), but for moderate impairment (eGFR 30–59 mL/min), the dose is reduced to one 150 mg

nirmatrelvir tablet and one 100 mg ritonavir tablet twice daily for 5 days. For severe renal impairment (eGFR <30 mL/min), a modified regimen is used: 300 mg nirmatrelvir with 100 mg ritonavir on Day 1, followed by 150 mg nirmatrelvir with 100 mg ritonavir once daily on Days 2–5. For patients on hemodialysis, dosing is the same as those with eGFR <30 mL/min and dosing should occur post-dialysis to optimize drug exposure [Paxlovid label].

Another key consideration is the availability and suitability of dosage forms for pediatric use. Paxlovid is currently available only as nirmatrelvir 150 mg and ritonavir 100 mg oral tablets, which are co-packaged in various dose packs. Per the package insert, these tablets must be swallowed whole and cannot be crushed or chewed, which may pose challenges for younger adolescents, those with swallowing difficulties, and those dependent on enteric feeding tubes. At present, there are no liquid formulations or alternative dosage forms approved, which limits administration to those children able to swallow tablets.

CONCLUSIONS AND RESEARCH NEEDS FOR NIRMATRELVIR/RITONAVIR

Overall, nirmatrelvir/ritonavir is a valuable therapeutic option for preventing progression to severe disease in high-risk adults, though application of these data to adolescents requires caution. Adolescents aged 12-17 years of age may benefit from treatment, but the absolute risk reduction is likely lower due to the milder disease course pediatric patients experience. There is a lack of data evaluating use of nirmatrelvir/ritonavir in patients under 12 years of age. The ongoing EPIC-Peds trial will provide data on safety, pharmacokinetics, and efficacy in children, but until those results are available, clinicians must rely on limited retrospective studies or extrapolated adult data. Future research should prioritize younger age groups and explore alternative formulations suitable for children.

REMDESIVIR

SUMMARY OF EVIDENCE FOR REMDESIVIR

Studies involving the use of remdesivir in hospitalized patients with COVID-19 [Beigel 2020, Sise 2024, Spinner 2020] have generally focused on adults age ≥18 years (Table 5, Supplementary Tables

1 and 2, Supplementary Figure 5). Two trials included children aged ≥12 years [Goldman 2020, Spinner 2020], but one focused only on treatment of severe COVID-19, and neither reported separately the number of participants aged <18 years or their associated outcomes (including adverse events). The key trial investigating an outpatient course of remdesivir to prevent hospitalization or death in high-risk patients (PINETREE study) included 8 participants between ages 12 and <18 years [Gottlieb 2022].

Table 5. GRADE Evidence Profile: In children with mild to moderate COVID-19, does treatment with remdesivir vs. no treatment result in better outcomes (e.g., time to symptom resolution, hospitalization, progression to severe or critical illness)?

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**remdesivir**	**no remdesivir***	**Relative (95% CI)**	**Absolute (95% CI)**		
Hospitalization (all-cause) (follow-up: 28 days)												
1[Gottlieb 2022]	randomized trials	not serious	not serious	serious[a]	serious[b]	none	5/279 (1.8%)	0.5%	**HR 0.28** (0.10 to 0.75)	**4 fewer per 1,000** (from 4 fewer to 1 fewer)	⨁⨁◯◯ Low	CRITICAL
				serious[a]	very serious[b]			3.0%		**22 fewer per 1,000** (from 27 fewer to 7 fewer)	⨁⨁◯◯ Low	
				not serious[a]	serious[b]			6.0%		**43 fewer per 1,000** (from 54 fewer to 15 fewer)	⨁⨁⨁◯ Moderate	
Covid-19-related medically attended visits (follow-up: 28 days)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	remdesivir	no remdesivir*	Relative (95% CI)	Absolute (95% CI)		
1[Gottlieb 2022]	randomized trials	not serious	not serious	not serious[a]	serious[b]	none	4/246 (1.6%)	21/252 (8.3%)	**HR 0.19** (0.07 to 0.56)	**67 fewer per 1,000** (from 77 fewer to 36 fewer)	⨁⨁⨁◯ Moderate	IMPORTANT
Symptom alleviation												
1[Gottlieb 2022]	randomized trials	not serious	not serious	not serious[a]	serious[b]	none	23/66 (34.8%)	15/60 (25.0%)	**RR 1.60** (0.74 to 3.48)	**150 more per 1,000** (from 65 fewer to 620 more)	⨁⨁⨁◯ Moderate	IMPORTANT
Serious adverse events												
4[Gottlieb 2022, Beigel 2020, Sise 2024, Spinner 2020]	randomized trials	not serious	not serious	not serious[a]	serious[b]	none	98/688 (14.2%)	77/612 (12.6%)	**RR 0.78** (0.61 to 1.00)	**28 fewer per 1,000** (from 49 fewer to 0 fewer)	⨁⨁⨁◯ Moderate	CRITICAL

CI: confidence interval; **HR:** hazard ratio; **RR:** risk ratio

*For hospitalization, percentages represent illustrative baseline risks for patients without risk factors for progression to severe disease, patients at increased but not high risk, and patients at high risk.

Explanations

a. Most trial participants were adults and evidence in pediatric patients is limited, reducing applicability to children. In addition, key trials were conducted in the pre-Omicron era and largely among unvaccinated, high-risk outpatients; current baseline risks and hospitalization patterns have changed substantially, which may affect applicability—particularly for lower-risk populations where hospitalizations are now rarer and less specific to COVID-19. Because the trial populations closely match those at highest risk today, the panel did not further downgrade for baseline-risk differences in the highest-risk stratum but did downgrade for indirectness in lower-risk strata.

b. Few events do not meet the optimal information size and suggest fragility in the estimate. For the outcome of hospitalization: at baseline risks of 0.5%, the entire 95% CI of the absolute risk difference is within the no effect boundary and only fragility is present (rated down once); at baseline risk of 3%, the 95% CI of the absolute risk difference includes appreciable benefits as well little or no effect on hospitalization: rated down twice (but leaving the overall certainty at

367 “low” due to borderline judgments in combination with the indirectness rating); at 6% baseline risk, the entire 95% CI of the absolute risk reduction is above the
368 panel determination of minimally important difference (rated down once)

BENEFITS OF REMDESIVIR

The PINETREE study was a randomized, double-blind, placebo-controlled trial that enrolled 562 non-hospitalized patients aged ≥12 years who had COVID-19 with symptom onset within the previous 7 days and ≥1 preexisting risk factor for progression to severe COVID-19 [Gottlieb 2022]. Eligible risk factors included age ≥60 and various coexisting conditions, the most common of which were diabetes mellitus (61.6%), obesity (55.2%), and hypertension (47.7%); immune compromise was present in 4.1% of participants. The mean age was 50 years. Patients were randomized to receive 3 days of intravenous (IV) remdesivir or placebo. The primary efficacy outcome, a composite of COVID-19-related hospitalization or any-cause 28-day mortality, occurred in 2 patients (0.7%) in the remdesivir group and 15 (5.3%) in the placebo group (hazard ratio, 0.13; 95% CI, 0.03 to 0.59). No deaths occurred by day 28. Results for the 8 patients aged 12 to <18 years were not reported separately.

HARMS OF REMDESIVIR

Pediatric remdesivir use is common, with real-world reports suggesting low adverse event rates [Goldman 2021, Gotzinger 2020, Player 2024]. The Clinical Administration of Remdesivir After COVID-19 Diagnosis in Children (CARAVAN) study, a phase II/III open-label, single-arm trial in 53 children who received remdesivir for a median duration of 5 days, revealed no new safety concerns [Ahmed 2024]. Transient elevations in transaminases are common, especially in those with preexisting hepatic conditions. However, these abnormalities are typically mild and self-limiting and can also be related to the SARS-CoV-2 infection itself, making causal inferences uncertain.

OTHER CONSIDERATIONS FOR REMDESIVIR

In the ambulatory setting, accessibility, and cost of remdesivir are significant considerations. There are limited avenues in pediatric care to provide IV administration for 3 consecutive days. Infusion centers typically serve a high proportion of patients with immunocompromising and other high-risk conditions, and these facilities may not be well-designed for patients with a contagious illness. Further,

access to IV infusion centers on weekends and holidays often presents a barrier. Many children must travel long distances to reach pediatric specialty care where infusions may be most available, and children residing in economically disadvantaged regions may be disproportionally impacted by lack of pediatric infusion centers [Brown 2023]. Finally, while precise cost-benefit analyses are not possible given that the benefits of remdesivir are poorly defined, the cost of remdesivir administration, including both the drug and the administration costs, are also significant.

CONCLUSIONS AND RESEARCH NEEDS FOR REMDESIVIR

Remdesivir has demonstrated benefit when given to ambulatory adults early during COVID-19, but data on its efficacy in pediatric patients are not available. Clinically significant benefits are most likely to be observed in pediatric patients who are at high risk for progressing to severe COVID-19. While the risk of remdesivir therapy appears to be low, cost and accessibility present obstacles, though there are no alternative treatments for children who are under 12 years of age or weigh less than 40 kg. Further research is needed to better identify the pediatric patients who are most likely to benefit from remdesivir and the magnitude of that benefit.

HOW TO APPLY GUIDELINES TO MANAGEMENT OF PEDIATRIC AMBULATORY PATIENTS WITH MILD TO MODERATE COVID-19

Table 6 provides an overview of the panel's recommendations for treatment of mild to moderate COVID-19, based on age and risk factors for progression to severe disease. Tables 1 and 2 list examples of relevant risk factors in pediatric patients.

Table 6. Approach to treatment of mild to moderate COVID-19 in infants, children, and adolescents

	Risk Factors for Progression to Severe COVID-19			
Age Group	None	1 associated with increased but not high risk[a]	Several associated with increased but not high risk[a]	≥1 associated with high risk[b]
Infant		Suggest remdesivir	Suggest remdesivir	Recommend remdesivir

(<12m)	Suggest against antivirals			
Child (12m to <12y)		Suggest against antivirals		
Adolescent (12y to <18y)			Suggest nirmatrelvir/ritonavir OR remdesivir	Recommend nirmatrelvir/ritonavir OR remdesivir

[a]See Table 1 for examples of factors associated with high risk of progression to severe COVID-19.
[b]See Table 2 for examples of factors associated with increased risk of progression to severe COVID-19.

Management decisions should also incorporate other patient- and pathogen-specific factors that may influence the choice of COVID-19 treatments. The assessment should include consideration of:

- Date of onset of symptoms
- Disease severity
- Pre-existing immunity from vaccination or recent infection
- Drug-drug interactions
- Ability to swallow tablets (for patients eligible for nirmatrelvir/ritonavir)
- Patient and family preferences and values, including weighing risks and benefits of therapies and, for remdesivir, considering logistical challenges of daily infusions for 3 days.

Timely initiation of antiviral therapies is critical as they are most efficacious when given as soon as possible and no later than 5 to 7 days after symptom onset. Some experts would consider remdesivir initiation >7 days after symptom onset in patients with immunocompromise. For pediatric patients with mild-to-moderate COVID-19 who are admitted to the hospital for another reason, it is reasonable to use the same approach as for non-hospitalized children.

RESEARCH NEEDS AND FUTURE DIRECTIONS

Important unanswered questions specific to pediatric treatment of mild to moderate COVID-19 include:

- What is the efficacy and safety of COVID-19 therapies approved or authorized by the US FDA for neonates, infants, and children?

- What are the pharmacokinetics of nirmatrelvir/ritonavir tablets when crushed or dissolved?
- Which sub-populations of children with COVID-19 benefit most from specific therapeutic agents?
- What is the efficacy and safety of COVID-19 therapies in children who are immune from prior SARS-CoV-2 infections or vaccination?
- What is the efficacy and safety of treatments for pediatric infections due to specific SARS-CoV-2 variants and sub-variants?
- What is the incidence of symptomatic SARS-CoV-2 rebound infection in children, and what is the efficacy and safety of antiviral therapy for these cases?
- How do therapeutic agents perform when compared with each other to allow a tiered approach to treating children with COVID-19?
- What are the comparative efficacy and safety of combinations of different drugs in treating different severities and clinical phenotypes of COVID-19?

Future studies should prioritize inclusion of children as well as address these uncertainties to enable a more definitive treatment approach to COVID-19.

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Additional Information: More detailed information on the analysis and development of the recommendation is available in the Supplementary Material.

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